RESPONDER ANALYSIS
According to Medical Officer Based on Available Lumbar BMD Data on Electronic File

	Placebo	6.5	12.5	15	25	Total Drug	Total
Baseline n	46	31*	30*	31	34*	126	172
Completers n (i.e, complete 24 mths)	19	16	17	20	21	74	93
Completers (LOCF – 6 mths)	34	25	24	24	27	106	140
Continuation rate – 24 mths	41%	52%	57%	67%	62%	59%	54%
Continuation rate – LOCF	74%	81%	80%	80%	79%	84%	81%
#subjects with BMD ≥1.7 % @ 24mths	5	8	11	12	17	48	53
#subjects with BMD ≥ 1.7% (LOCF)	5	13	16	16	23	67	72
Bioeffectiveness rate @ 24 mths	26%	50%	65%	60%	81%	65%	57%
Bioeffectiveness rate LOCF	15%	52%	62%	67%	85%	63%	51%
%subjects with BMD ≥ 1.7 % (24 mths)	11%	26%	37%	40%	50%	38%	31%
%subjects with BMD ≥ 1.7 % (LOCF)	11%	42%	50%	54%	67%	53%	41%

Assumptions and Definitions:

1) Effect size = %BMD change on drug – average %BMD change on placebo .
2) An effect size ≥ 4% was used to establish sample size for this NDA, based on the data from Estraderm.
3) Average %BMD change on placebo (LOCF)= -2.3% (per sponsor ITT analysis).
4) Therefore, subject is included as responder if %BMD change(LOCF) ≥ 1.7%.)
5) Three subjects (301013 (6.5 cm^2), 309006 (12.5 cm^2), 307014 (25 cm^2)) had inadequate baseline lumbosacral spine BMD measurements and are excluded from this analysis (for a final n of 172 rather than 175)

Continuation rate = (# completers at given time in trial [e.g., at 6mths for sponsor LOCF analysis or 24 mths])divided by (# subjects at baseline)

Bioeffectiveness rate = biological response among those who use it.

Continuation rate x Bioeffectiveness rate = Percent of Subjects who Responded (or %subjects with BMD ≥ 1.7 % (at 24 months or LOCF/endpoint).

ANALYSIS of TREATMENT GROUPS BY CHI-SQUARE

Lumbar Spine BMD Responders vs. Non-Responders
Comparison of Each Treatment Group to Placebo

	#Responders	#Non-Responders	Total
6.5 cm^2	13	19	32
Placebo	5	41	46
Total	18	60	
p-value – pairwise comparison of drug and placebo groups (Fisher's exact test)			P=0.003

	#Responders	#Non-Responders	Total
12. 5 cm^2	16	15	31
Placebo	5	41	46
Total	21	56	
p-value – pairwise comparison of drug and placebo groups (Fisher's exact test)			P<0.001

	#Responders	#Non-Responders	Total
15 cm^2	16	15	31
Placebo	5	41	46
Total	21	56	
p-value – pairwise comparison of drug and placebo groups (Fisher's exact test)			P<0.001

	#Responders	#Non-Responders	Total
25 cm^2	23	12	35
Placebo	5	41	46
Total	28	53	
p-value – pairwise comparison of drug and placebo groups (Fisher's exact test)			P<0.001

Assumptions:

1) All (175) randomized subjects were included in this analysis.
2) Responder is defined as subject with percent change in lumbar spine BMD $\geq$ 1.7% at 24 mths or LOCF. Effect size (i.e., difference between [drug change from baseline] and [placebo change from baseline]) is defined as $\geq$ 4%, the assumption made by the sponsor in designing this protocol, which was based on Ciba-Geigy data for Estraderm. The placebo chane from baseline was –2.3% in the sponsor's ITT analysis.
3) If a subject had no baseline or followup lumbar spine BMD data, he was classified as a non-responder.

Note: 1) The sponsor also provided a responder analysis for the lumbosacral spine BMD change. However, the sponsor's analysis was based on a more conservative assumption – a BMD change of zero.

2) The study was not designed to compare the four drug treatment arms. The data suggest a linear dose response curve and a greater number of responders at higher doses of estradiol.

After reviewing this responder analysis with the statistical team, the statistical team recommended a third, even more rigorous, chi-square responder analysis (see Table entitled "Analysis of Treatment Groups by Chi-Square") (page 21). In this analysis, data was converted from a continuous to a categorical format. Subjects with lumbosacral spine BMD change ≥ 1.7 % were defined as responders and all subjects with missing data were defined as nonresponders. The significance of these chi-square responder analyses was tested by Fischer's exact test. In this analysis, the number of responders in the treatment groups was statisitically different from the number of respondrs in the placebo group. These three sets of analyses of the lumbosacral spine BMD change – the sponsor's ITT and the confirmatory analyses with imputed data, the medical officer's responder analysis, and the chi-square responder analysis confirmed the observed change in the primary efficacy variable.

Secondary Efficacy Analyses

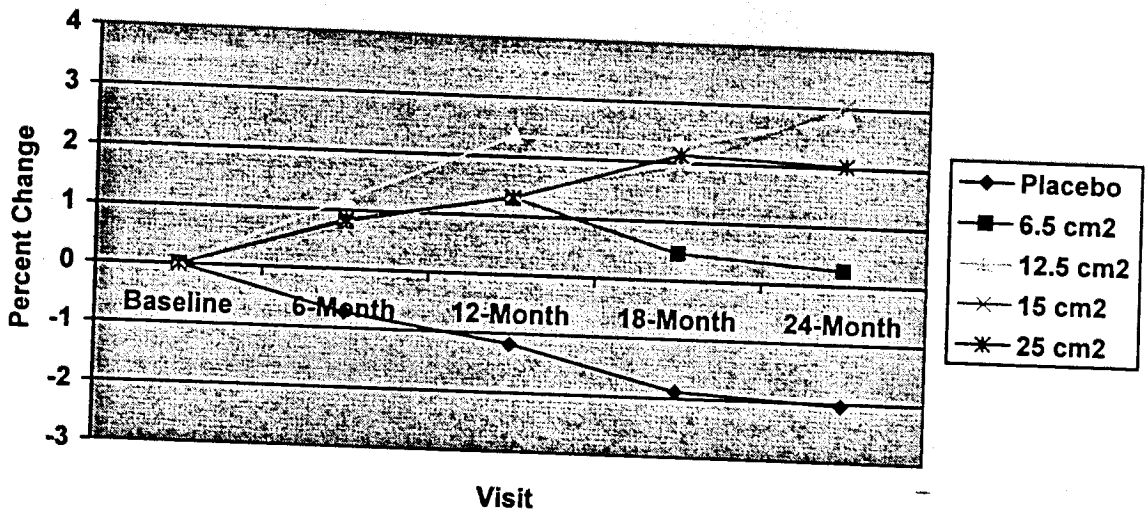
Although not included as a variable in the original protocol, an amendment to the protocol (in 1996) added the total hip as a secondary efficacy variable. Statistically, significant changes were observed in the sponsor's ITT analysis (again including only subjects with 6 months data as opposed to all randomized subjects). These changes were confirmed by analyses with zero and placebo change imputed for those subjects with missing data. The following tables and graphs are excerpted from the statistician's summary.

Sponsor's Analyses on Percent Change in BMD of Total Hip

Mean Percent Change From Baseline in BMD (g/ cm^2) of Total Hip by Treatment and Visit (Sponsor's ITT)

Treatment Group		6 months	12 months	18 months	24 months	Endpoint
Placebo	N/Mean	34/-0.73	26/-1.17	22/-1.89	21/-2.04	34/-1.66
6.5 cm^2	N/Mean	23/0.81	18/1.31	16/0.47	14/0.26	23/0.65
	p-Value	0.014	0.001	0.011	0.020	0.004
12.5 cm^2	N/Mean	24/1.19	22/2.35	18/2.31	18/2.85	24/2.41
	p-Value	0.002	<0.0001	<0.0001	<0.0001	<0.0001
15 cm^2	N/Mean	23/0.71	22/1.38	21/1.94	20/3.05	23/2.61
	p-Value	0.018	0.0003	<0.0001	<0.0001	<0.0001
25 cm^2	N/Mean	24/0.84	22/1.31	22/2.13	21/2.03	25/1.98
	p-Value	0.013	0.0003	<0.0001	<0.0001	<0.0001

Figure 2. Sponsor's Analyses on Percent Change in BMD of Total Hip



Revised ITT Analyses I on Percent Change in BMD of Total Hip (0 [zero] Change Imputed)					
Mean Percent Change From Baseline in BMD (g/ cm^2) of Total Hip by Treatment and Visit (Revised ITT Analysis, Approach I)					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.54	46/-0.89	46/-1.18	46/-1.23
6.5 cm^2	N/Mean	32/0.58	32/0.67	32/0.45	32/0.47
	p-Value	0.010	0.001	0.008	0.009
12.5 cm^2	N/Mean	31/0.92	31/1.77	31/1.86	31/1.87
	p-Value	0.001	<0.0001	<0.0001	<0.0001
15 cm^2	N/Mean	31/0.53	31/1.05	31/1.41	31/1.94
	p-Value	0.016	<0.0001	<0.0001	<0.0001
25 cm^2	N/Mean	35/2.42	35/3.04	35/3.56	35/4.01
	p-Value	0.01	0.0002	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

Revised ITT Analyses II on Percent Change in BMD of Total Hip (placebo change imputed)					
Mean Percent Change From Baseline in BMD (g/ cm^2) of Total Hip by Treatment and Visit (Revised ITT Analysis, Approach II)					
Treatment Group		6 months	12 months	18 months	24 months
Placebo	N/Mean	46/-0.72	46/-1.29	46/-1.94	46/-2.05
6.5 cm^2	N/Mean	32/0.39	32/0.25	32/-0.30	32/-0.34
	p-Value	0.013	0.003	0.013	0.015
12.5 cm^2	N/Mean	31/0.76	31/1.46	31/1.26	31/1.27
	p-Value	0.0015	<0.0001	0.0001	<0.0001
15 cm^2	N/Mean	31/0.15	31/0.73	31/0.87	31/1.37
	p-Value	0.019	0.0002	<0.0001	<0.0001
25 cm^2	N/Mean	35/0.36	35/0.50	35/0.84	35/0.75
	p-Value	0.015	0.0004	<0.0001	<0.0001

P-values are for comparisons of each dose against placebo. All of the p-values remained significant after adjusting for multiple comparisons using the Hochberg method.

The baseline measures and percent changes at LOCF/endpoint for the secondary variables are summarized in the Table entitled "Secondary Efficacy Outcome Measures" (page). The listed p-values reflect comparison of drug treatment groups to placebo. Thus, the observed changes in the secondary efficacy variables – total hip BMD, femoral neck BMD, and nondominant radius BMD, the bone markers – serum osterocalcin and urinary deoxypyridinoline/creatinine and urinary pyridinoline/creatinine ratios, though progressively less statistically significant, confirmed the primary efficacy outcome.

Calcium Intake

Even though a calcium intake of 1500 mg/day was recommended in diet and supplementation with calcium tablets supplied by the sponsor, the majority of subjects had a total calcium intake below 1000 mg/day, independent of location , as assessed by the study dietician. The data from the three centers that supplied the greatest number of study subjects is summarized below:

Secondary Efficacy Outcome Measures
Intent-to-Treat Analyses at Last Observation Carried Forward (LOCF or endpoint)
(Abstracted from Sponsor's Report- Text Tables 11,17,18,19,20,21,22,23,24,25,27,28,30)

Treatment	Placebo	6.5 cm^2 Climara	12.5 cm^2 Climara	15 cm^2 Climara	25 cm^2 Climara	Total
N randomized	46	32	31	31	34	175
Baseline total hip BMD (g/cm^2)	0.95	0.98	0.93	0.91	0.94	0.94
Percent change (%)	-1.66	0.65	2.41	2.61	1.98	
N	34	23	24	23	25	164
P value		0.0044	<0.0001	<0.0001	<0.0001	
Baseline femoral neck BMD ($g/^{cm2}$)	0.89	0.90	0.86	0.87	0.86	0.88
Percent change (%)	-0.95	-0.89	1.80	0.85	1.54	
N	34	26	24	25	28	173
P value		0.9482	0.0300	0.1286	0.0265	
Baseline nondominant radius BMD (g/cm^2)	0.81	0.83	0.79	0.79	0.81	0.81
Percent change (%)	-0.90	0.21	-0.18	-0.38	0.87	
N	34	26	24	25	27	
P value		0.0966	0.2349	0.4218	0.0123	
Baseline serum osteocalcin (ng/ml)	3.4	3.6	3.2	3.1	3.6	3.4
Percent change (%)	19.6	-19.2	-15.2	-10.4	-29.2	
N	35	25	19	26	28	159
P value		<0.0001	0.0032	0.0056	<0.0001	
Baseline urinary deoxypyridinoline/creatinine ratio (nmol/mmol)	19.6	17.0	18.2	17.0	17.5	18
Percent change (%)	16.4	-24.8	-22.2	-10.7	-21.4	
N	30	25	19	25	24	157
P value		0.0173	0.0271	0.237	0.0224	
Baseline urinary pyridinoline/creatinine ratio (nmol/mmol)	69.3	58.7	63.1	62.1	57.5	62.5
Percent change (%)	9.4	-18.2	-14.7	-9.5	-15.4	
N	35	26	23	28	28	165
P value		0.0849	0.0254	0.0787	0.0595	

Definitions:

Percent change refers to change from baseline at last observation carried forward or endpoint, expressed as %

P value refers to p value for pairwise treatment – placebo comparison at last observation carried forward (LOCF) or endpoint

Calcium Intake During Randomized Controlled Clinical Trial (Sponsor Report 97034) Sample of 3 Study Sites (Per Medical Officer)						
	Baseline Calcium Intake			Final Calcium Intake		
Site	<500 mg/d	500-1000 mg/d	>1000 mg/d	<500 mg/d	500-1000 mg/d	>1000 mg/d
301 (Henry, Utah)	5	14	2	5	10	4
309 (Weiss, CA)	11	15	12	9	12	6
304 (Gordon, OH)	9	7	0	3	8	1
Total of 3 sites	26	36	14	17	30	11
%	34%	48%	18%	29%	52%	19%
Summary	82% (<1000 mg/d)			81% (<1000 mg/d)		

8.2.3.4.3 Safety

APPEARS THIS WAY
ON ORIGINAL

Study Discontinuations

A total of 78 subjects (53 active drug; 25 placebo) withdrew from the study. The reasons for withdrawal, whether adverse events (AE) or more administrative, were distributed through all treatment groups and are outlined in the table below:

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ON ORIGINAL

STUDY DISCONTINUATIONS According to Medical Officer, Per Review of CRFs for Subjects with AE Numbers listed under the different treatment groups refer to number of subjects							
Reason for Withdrawal	**P**	**6.5 cm^2**	**12.5 cm^2**	**15 cm^2**	**25 cm^2**	**Total Drug**	**Total**
Adverse Event (total)	**6**	**5**	**3**	**5**	**4**	**17**	**23**
Types of Adverse Events							
Application site reactions	1	1	1	2	1	6 (35%)	
*(Also had application site reactions)	1	1	1	1*	–	*8(47%)	
Mood swings/depression				1*			
Nausea/lightheadedness/breast tenderness					1		
Joint pain	2				1		
Pelvic pain, breast tenderness	3				1		
Hot flushes			1				
Vaginal irritation, dyspareunia							
Colon cancer metatastatic to bladder	1						
Angina, hypertension (CRF not provided; withdrawal attributed to administrative "other" category per sponsor)							
Administrative	**12**	**6**	**6**	**1**	**7**	**20**	**32**
Unaccounted	**7**	**6**	**4**	**3**	**3**	**16**	**23**

Comments:

1) Adverse events includes 3 cases in addition to 20 described by sponsor as reasons for withdrawal. Many of these withdrawals secondary to adverse events (%) were because of application site reactions and occurred early in the clinical trial – usually by the time of the second or third visit. (Note: CRFs were only provided for subjects with adverse events as reasons for withdrawal.)
2) There were two serious AE that accounted for withdrawal: 307001 – development of angina and hypertension; 309006 diagnosis of colon cancer. Two other serious adverse events occurred (301019 – 15 cm2 - slipping off a ladder with resulting 3 fractured ribs and a 305007 – 15 cm2- punctured lung and a basal cell cancer of the lower lip), but both subjects continued and completed the study.
3) **'Administrative'** includes relocation, lost to followup, loss of study medication.

4) **'Unaccounted'** refers to subjects who withdrew because of protocol deviation, lack of efficacy, and withdrawal of consent. These subjects were not individually accounted for by the medical reviewer.

There were no deaths during this study and the four serious adverse events did not appear to be directly related to the drug effect. No breast cancers were observed during the study. Mammograms were obtained at baseline for all subjects and at end of study for 105 subjects. There were eight transitions from normal to abnormal mammography reports during the study, and seven transitions from abnormal to normal.

No vertebral fractures were described. However, x-ray of spine was done at baseline and subsequently only if a fracture was clinically suspected. Thus, an occult, asymptomatic fracture could be missed, particularly since height was measured only at baseline.
Four traumatic fractures occurred during the study, as outlined in the table below:

Traumatic Fractures

Subject #	Treatment	Cycle	Site	Cause	Baseline BMD: Lumbosacral Total Hip Femoral Neck Radius (g/cm^2)	% change (%)
310007	6.5 cm^2	6	4th left toe	Tripped; stubbed toe	0.858 0.728 L 0.592 L 0.633 L completed 24 months	9.9 6.0 3.6 3.6
301019	15 cm^2	3	Ribs	Fell off ladder	1.012 0.799 L 0.754 L 0.858 L completed 24 months	1.3 5.9 0 -1.3
304008	25 cm^2	9	Left radius	Rollerblade accident	1.369 0.952 L 0.890 L 0.909 L completed 12 months	2.3 1.8 -3.8 ---
311014	Placebo	1	Rib	fell	1.309 1.179 L	-0.9 -0.9

					1.113 L 0.850 L completed 24 months	-1.3 0.6
Data abstracted from text table 55 and individual subject BMD reports. L = left side						

Since this population was selected not to be osteoporotic, fractures secondary to osteoporosis were thus less likely in a two-year followup. If one looks at the individual bone densities, these subjects were in the general range and not at the extreme points, thus making osteopenia a less likely contributing factor to the fracture.

There were no significant changes observed in weight or blood pressure at two years, except at specific timepoints as cited below:

Changes in Weight and Blood Pressure (Abstracted from Sponsor's Report)					
Treatment	**P**	**6.5**	**12.5**	**15**	**25**
Baseline weight (lbs)	**163.2**	**161.0**	**167.4**	**158.4**	**165.4**
Mean change at 2 yrs (lbs)	**-2.8**	**1.9**	**1.4**	**6.0**	**-1.7**
N	**21**	**16**	**20**	**22**	**22**
Baseline Systolic BP (mm Hg)	**121**	**120**	**126**	**121**	**127**
Mean change at 2 yrs (mm Hg)	**-1**	**1**	**-6**	**2**	**-8**
Baseline Diastolic BP (mmHg)	**77**	**77**	**78**	**77**	**78**
Mean change at 2 yrs (mm Hg)	**-1**	**0**	**-3**	**2**	**0**

Comments:

There were no significant changes in weight in the treatment groups as compared to placebo.

Significant differences in systolic blood pressure were noted during the randomized clinical trial as follows:

Treatment Group	Cycle	Change
12.5	13	-8.2

12.5	16	-5.7
15	9	-4.4
25	6	-6.3

No statistically significant changes in the lipid profile weree observed, as outlined in the table below:

Changes in Lipid Profile (Abstracted from Sponsor's Report)					
Treatment	**P**	**6.5**	**12.5**	**15**	**25**
N	**21**	**16**	**20**	**21**	**22**
Screening Total Cholesterol (mg/dl)	**225**	**228**	**231**	**230**	**225**
Change at 2 yrs (mg/dl)	**-2**	**-6**	**-8**	**-6**	**-16**
Triglyceride	**135**	**128**	**124**	**141**	**125**
Change at 2 yrs (mg/dl)	**16**	**0**	**6**	**25**	**-6**
HDL Cholesterol (mg/dl)	**55**	**54**	**52**	**53**	**56**
Change at 2 yrs (mg/dl)	**3**	**4**	**3**	**2**	**2**
LDL Cholesterol (mg/dl)	**148**	**153**	**159**	**154**	**150**
Change at 2 yrs (mg/dl)	**-8**	**-10**	**-12**	**-12**	**-17**

Comments:

1) The sponsor reports that 6 subjects had significant elevations in lipid values:

Lipid measurement	N	Reported Ranges	Normal Ranges
Total Cholesterol	5	291-369	140-261 and 156-300
Triglyceride	4	293-593	44-213
LDL Cholesterol	2	232-243	63-231

Note the high normal ranges, particularly for total cholesterol and LDL cholesterol. Current usual normal total cholesterol is below 200 mg/dl and LDL cholesterol is below 130 mg/dl.

2) No significant changes between treatment groups and placebo were observed.

No significant hematological abnormalities were observed. Only a few abnormal LFT's were summarized by the sponsor, and only one patient had an abnormal glucose, though still within the inclusion criteria for this clinical trial. It is unclear if this glucose value is fasting or random. Five subjects had LFT elevations which were considered "clinically significant" and possibly

related to study drug by the investigators. These subjects were enrolled in P (n=1), 12.5 cm^2 (n=1), 15 cm^2 (n=3) treatment groups. See table below.

Chemistry: Liver Function Tests and Glucose Abnormalities (Abstracted from Sponsor's Report)		
LFT	**'clinically significant' range**	**Normal range**
ALT (U/L)	61-168	6-34
AST (U/L)	48-69	9-34
GGT	4-49	88-207

Comments:

1) From this description, it is unclear how many total LFT abnormalities were present, which were not considered "clinically significant" by the individual investigators. A more complete report of abnormal LFT values as well as baseline values for these subjects has been requested from the sponsor.

2) Since so many different factors can be reflected in elevated transaminase values, it is difficult to ascribe causality. However, an association needs to be considered if there is a change from baseline and if no other intercurrent events are cited.

9-10 Overview of Efficacy and Safety Conclusions

General Comments

The sponsor has shown efficacy of the four active drug Climara estradiol patches (6.5, 12.5, 15, 25 cm^2) for the prevention of postmenopausal osteoporosis in a randomized, placebo-controlled, parallel, two-year study, despite a large number of dropouts (78/175 or 45%), a relatively small n of completers (25, 23, 25, 27, respectively, contributed to the endpoint or LOCF analysis, but only 16, 18, 20, 21, respectively, completed 24 months in each group), and an even greater relative number of dropouts in the placebo group (34/46 had data at 6months; but only 21/46 completed 24 months of the study). Trabecular bone mineral density, as reflected in the spinal and to some extent total hip BMD measurements, increased, as did cortical bone, as reflected in the mid-shaft of the radius and femoral head BMD measurements. The percent changes in lumbosacral BMD (LOCF) were 2.32, 3.74, 3.45, 5.20 % for the four treatment doses, respectively, as opposed tot –2.33% for the placebo group. There was an observed decrease in bone formation, as reflected in the decrease in osteocalcin measurements, and also a decrease in bone resorption, as reflected in the decrease in urinary pyridinoline/creatinine and deoxypyridinoline/creatinine ratios.

Some of the observations and limitations of this NDA study protocol as applicable to clinical practice are outlined below:

1) The main goal in the prevention of osteoporosis is the prevention of fractures, particularly hip fractures. This study did not include a population at high risk for fracture, and it was not designed to observe an effect on the fracture rate.

2) The selected study population did not have osteoporosis. Thus, the study protocol only looked at the question of prevention and not treatment of osteoporosis. Since much of clinical medicine revolves around diagnoses that can be coded in ICD-9 codes, often an established diagnosis of osteoporosis is required before treatment for osteoporosis is initiated. The data provided in this NDA do not reflect the role of transdermal estradiol in the treatment of established osteoporosis.

3) The subjects all had had hysterectomies. Thus, they were treated continuously with estrogen without progesterone-induced withdrawal. Conversely, the majority of postmenopausal women have not undergone hysterectomies. Safety data regarding cyclical estrogen and progesterone or combined estrogen-progesterone using the Climara patch as an estrogen source is thus unavailable.

4) Exercise and dietary vitamin D and calcium supplementation are common clinical recommendations for the prevention and treatment of postmenopausal osteoporosis. There were no recommendations for exercise in this protocol, women with known vitamin D deficiency were excluded, though serum vitamin D levels were not actually measured, and no vitamin D supplementation was offered. Though a daily calcium intake of 1500 mg was recommended, the dieticians' assessments indicated that most subjects had inadequate daily calcium intake.

The study in this protocol does confirm that transdermal estrogen is effective in the prevention of postmenopausal osteoporosis, as has been previously demonstrated for Estraderm, which also provides ethinyl estradiol transdermally. Estraderm represents ethinyl estradiol in a alcohol base in a reservoir rather than in a matrix. This difference and the application of the Climara patch every 7 days (rather than every 3.5 days for the Estraderm patch) may account for some of the differences observed between this study and the prior study, on the basis of which Estraderm was approved.

Comparison of Climara Clinical Trial to Estraderm Clinical Trial

Although it is not possible to draw a direct comparison between two separate studies done at different times, the Climara clinical trial was similar to the Estraderm double-blind, placebo controlled, randomized two year clinical trial in duration and number of subjects. The study population in the Estraderm trial comprised women who had undergone abdominal hysterectomy and bilateral oophorectomy 6 weeks to 24 months prior to study entry, which may partially account for the higher lumbosacral BMD. Perhaps the more sustained estrogen concentrations in the climara seven-day preparation partially account for the slightly higher percent change in lumbosacral spine BMD. The results for the two separate studies are summarized below:

Summary of Sponsor's Climara Intent-to-Treat Endpoint Analysis Lumbar Spine BMD (Abstracted per Medical Officer)						
Treatment	**P**	**6.5 cm^2 0.025 mg/24h**	**12.5 cm^2 0.05 mg/24h**	**15 cm^2 0.06 mg/24 h**	**25 cm^2 0.1 mg/24h**	**Total**
Baseline N/LOCF N	**46/34**	**31/25**	**30/24**	**30/24**	**34/27**	**172/93**
Amount Estradiol (mg/24h)	**0**	**0.025**	**0.05**	**0.075**	**0.1**	
Baseline BMD	**1.13**	**1.12**	**1.10**	**1.09**	**1.12**	**1.11**
S.D.	**0.20**	**0.22**	**0.16**	**0.12**	**0.16**	**0.18**
Change in lumbar spine BMD (%)	**-2.33**	**2.32**	**3.74**	**3.45**	**5.20**	
Climara-Placebo pairwise p-values		**<0.001**	**<0.001**	**<0.001**	**<0.001**	

Summary of Estraderm Intent-to-Treat Endpoint Analysis Lumbar Spine BMD (Abstracted from Statistical Review of NDA 19-081/S-018 Study 05 per D. N. Marticello, PhD 7/11/90)				
Treatment	**P**	**0.025 mg/24 h**	**0.05 mg/24 h**	**0.1 mg/24 h**
N 127 enrolled; 102 completed	**35**	**23**	**23**	**21**
Baseline BMD	**1.21**	**1.18**	**1.21**	**1.22**
Change in lumbar spine BMD (%)	**-5.44**	**-3.29**	**1.03**	**3.41**
Estraderm – Placebo pairwise p-values		**0.122**	**<0.001**	**<0.001**

In addition, the Estraderm NDA consisted of two studies: Study 05 summarized above and Study 06, a double blind, randomized parallel study to determine the safety and efficacy of Estraderm 0.1 mg in a cyclic regimen with medroxyprogesterone for the prevention of progression of vertebral fractures in 76 osteoporotic women, ages 45-75.

In a published study comparing the effects of continuous esterified estrogens (0.3, 0.625, 1.25 mg/day) in 406 postmenopausal women [128 had and 278 had not undergone hysterectomy, though the demographics between the two groups did not differ significantly], Genant et al (Arch Intern Med 157:2609-2615, 1997) observed mean increases in

lumbosacral spine bone mineral density by DEXA at 2 years comparable to those observed in this Climara study: 1.8, 2.8, 5.1 % change, respectively, as compared to a –2.5% decrease in the placebo group. Of note, there was only 1/59 (1.7%) incidence of endometrial hyperplasia in the 0.3 group as opposed to 17/59 (28.2%) in the 0.625 mg group and 32/60 (53.3%) in the 1.25 mg group. Similarly, raloxifene (Evista) was approved for the prevention of osteoporosis on the basis of a 2% increment in lumbar spine and hip bone mineral density by dual-energy x-ray absorptiometric (DEXA) measurements, as compared to a 1% decrement in the calcium-supplemented placebo group.

6) For chronic therapy, such as the prevention of osteoporosis, the lowest effective dose is preferable. The effect observed with the lowest patch (6.5 cm^2)is comparable to the effects observed in other preparations approved for osteoporosis prevention.
The clinical caveats from this study, however, suggest that a greater effect may be achieved with a higher dose and that a larger number of women, proportionately, may respond to the higher dose. Thus, it would be important to document the effect of a given Climara dose on prevention of osteoporosis in an individual woman with bone mineral density and urinary pyridinoline studies.

7) Since the submitted physician labeling was very general, more specific details regarding the study population and design of the randomized clinical trial were included in the label, in order to make this information more readily available to the practicing physician. A patient information label was not submitted in the NDA; this label had been amended in 1996 and ironically already listed the osteoporosis prevention indication. Apparently, a general patient information label for all estrogen products was approved by HFD580 at that time.

8) In future clinical trials in osteoporosis, it may be helpful to correlate change in lumbosacral BMD to more easily available data such as change in (carefully-measured) height. Height was only measured at baseline in this trial.

Division of Scientific Investigation Report

Since concern about one of the study sites was raised by DSI, the events are briefly summarized in this report. On 12/9/98, Dr. H.W. Ju from the Division of Scientific Investigation, reported a discrepancy in 13/23 subjects at site 301 (Daniel C. Henry, M.D., Salt Lake City, Utah) between the reported values in the NDA Compliance Records submitted by Berlex to the FDA and the clinical investigator's records (CRFs, Source Data, Drug Inventory Records, etc). Review of Dr. Ju's report indicated that the sponsor had incorrectly transcribed information from the clinical investigator's records referring to compliance with the regimen of returning used and unused patches that is outlined in the protocol. See summary notes from Dr. Ju's report, which are attached in the Appendix. See also the attached table, which identifies the subjects with discrepancies, and lists the data for the primary efficacy variable, lumbar spine BMD at baseline, 6, 12, 18, 24 months, and % change in lumbar spine BMD at 6, 12, 18, 24 months. The discrepancies are distributed through all treatment groups (P 3/7, 6.5 cm^2 2/4, 12.5 cm^2 ¾, 15 cm^2 2/4, 25 cm^2 ¾, [subjects with discrepancies/total subjects in treatment group at site 301]). There do not appear to be gross differences in the primary efficacy measures of subjects with

discrepancies as compared to subjects without discrepancies. In addition, an analysis of the data without site 301 revealed similar major conclusions, with persistence of significant p-values. On 2/12/99, Dr. Ju called the medical reviewer and reported that the investigation is continuing and that his final report would probably be available in the following week. On 12/17/99, Dr. Ju received an explanation from Berlex, which he described as "acceptable", explaining the discrepancies observed. Dr. Ju's DSI report and the sponsor's report, as well as a listing of subjects in site 301 are included in the appendix.

11 Resistance

As noted in the Responder analysis (Section 8.2.3.4.2 Clinical Efficacy), 42 – 67% of the subjects on active drug were classified as responders. Calcium and vitamin D deficiency may have contributed to this low response rate and apparent resistance.

12 Labeling Recommendations

The major concerns about the sponsor's label are that the actual clinical trial performed for FDA approval for the indication of osteoporosis prevention is described in very general terms and the graphs of the sponsor's Intent-to-Treat (ITT) analyses do not point out that these analyses were not true ITT analyses in that they omitted 25% of the randomized population, i.e., those subjects whose data was unavailable at 6 months. The previously approved label for Climara for vasomotor symptoms appears to have been amended by the sponsor to include some of the wording from the draft estrogen drug product labeling (9/8/98) and also to include the pharmacokinetics data submitted in this NDA. These changes have resulted in an unclear juxtaposition of concepts, particularly in the pharmacokinetics section. The attached corrected label draft attempts to clarify the actual data in this NDA on which approval is based. Specific additional comments/corrections are listed below: (Page numbers refer to page numbers on Berlex Climara label.)

(1) Pages 2-5: pharmacokinetics section needs rewriting to assure a more fluid transmission of concepts and data;
(2) Page 4: time below graph should be in hours not minutes; Comment regarding dose proportionality of 6.5 and 12.5 cm^2 patches has been added and original wording has been altered.
(3) Page 6: ? obesity – as special population – consider addition of comment, pending response of sponsor regarding relation of weight and observed estradiol levels;
(4) Page 7, Paragraph 5: Postmenopausal is added before osteoporosis; indication is prevention (not treatment or management) based on the studied population; "hysterectomized, postmenopausal women" replaces "subjects."
(5) Page 7: Table 2 – numbers do not match the numbers for the primary efficacy outcome measure, lumbosacral spine bone mineral density;
(6) Pages 8 and 9: Comment is added "Subjects with missing 6 months data were not included in Intent-to-Treat Analysis."
(7) Page 10, Table 3: amount of estradiol (0.025, 0.05, 0.06, 0.1 mg/day) is added to descriptions of treatment.

(8) Page 10, Table 3: Include femoral neck data in table, at 12 and 24 months, to the right of total hip data.
(9) Page 12: Comments added re HERS study: "Observational studies have suggested a benefit. However, a randomized, double-blinded, placebo-controlled clinical trial (Heart and Estrogen/progestin Replacement Study (HERS)) showed no benefit of conjugated estrogen plus progestin therapy in 2763 postmenopausal women with established coronary disease." Although a negative study, the HERS study information is important and should be included in estrogen product labels. In the labeling discussion with the HFD580 group on 2/18/99, there was agreement about this point, but it was pointed out that the innovator in the estrogen field needs to include this study in its label first, so that a competitor such as Berlex would not have an unfair disatvantage. Thus this comment was not included in the label.
(10) Page 13. Sentence was to be deleted, to follow the HERS study statement:"Thus, ongoing and future large scale randomized trials may fail to confirm this apparent benefit."
(11) Page 15: Adverse Reactions – The following phrase is added: "Patients with known skin irritation to the patch were excluded from participation in the studies."
(12) Page 16: Comment added: "Use of the patch while swimming, bathing, or using a sauna has not been studied and should be avoided."
(13) Page 17: Clarification of indication of Climara for vasomotor symptoms vs for osteoporosis.
(14) Page 17: The sentence "The choice of which dose to use should be made on the basis of individual considerations such as the age of the patient, other risk factors for osteoporosis and response to therapy as assessed by biochemical markers" has been modified to "Response to therapy can be assessed by biochemical markers and measurement of bone mineral density." The deleted comments are vague and not directly substantiated by data in NDA.

Upon further discussion with Drs. Sobel and Troendle after the labeling meeting, the section describing the clinical trial was shortened, in accordance with other labels such as the Estraderm label, and moved from the indications section to the clinical pharmacology section. The label version forwarded to the sponsor is attached in the Appendix.

13 Recommendations

13.1 Approval – see outstanding concerns below.

The clinical pharmacology, statistical, and medical reviews concur that the data provided overall support the sponsor's request for an indication for approval of Climara patch for the prevention of postmenopausal osteoporosis. However, the following concerns need to be clarified before approval can be granted:

(1) On 2/12/99, the clinical pharmacology group raised the question "does obesity affect response of lumbosacral spine BMD response to the transdermal patch?" Specifically, are there enough supporting data to approve the 6.5 cm^2 patch for obese women? The question has been referred to the sponsor, and the data will also be be further analyzed by the FDA medical and pharm. Reviewers after it is provided by the sponsor.

(2) The Division of Scientific Investigation has raised questions about one study that contributed 23 subjects to the study (see summary). The final report from DSI is still pending.

(3) Changes need to be made in the labeling, as requested by the FDA.

SELECTED REFERENCES:

Draft Osteoporosis Guidance: "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis", 1994

E9 Statistical Principles for Clinical Trials, Federal Register, Vol. 63, No. 179, 49583-98, 9/16/98

Genant HK et al (Estratab/Osteoporosis Study Group). Low-Dose Esterified Estrogen Therapy. Arch Intern Med 157: 2609-2615, 1997

Hulley S et al (Heart and Estrogen/progestin Replacement Study (HERS) Research Group). Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. JAMA 280:605-613, 1998

Pettiti D. Hormone Replacement Therapy and Heart Disease Prevention: Experimentation Trumps Observation. JAMA 280: 650-652, 1998

Raloxifene (Evista) Approved Label

/S/

Joanna K. Zawadzki, M.D., F.A.C.P.

Concurrence:

/S/

Gloria Troendle, M.D.
Team Leader

Distribution:
Archival:HFD580/NDA20-375
HFD510/Sobel/Troendle/Sahlroot/Kavanagh/Ahn/Hedin/Zawadzki
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Appendixes
NDA 20994

Annotated Label Sent to Sponsor

APPEARS THIS WAY
ON ORIGINAL

19 pages

DRAFT

LABELING